REMARKS

Claims 20-33 are pending and under examination in the subject application. Applicants have hereinabove amended claims 20, 23, 25, 28, 30 and 31. Applicants maintain that these amendments raise no issue of new matter and respectfully request entry of this Amendment. Upon entry of this Amendment, claims 20-33 will still be pending and under examination.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the November 14, 2005 Office Action have been overcome and respectfully request that the Examiner reconsider and withdraw same.

Rejection Under 35 U.S.C. §103(a)

Jayadev et al. in view of Mycek et al.

The Examiner maintained the rejection of claims 20, 25, 26, 30 and 31-33 under 35 U.S.C. §103(a) as allegedly unpatentable over Jayadev et al. in view of Mycek et al., and U.S. Patent Nos. 5,597,830 and 6,147,060.

In response to the Examiner's rejection, applicants respectfully traverse and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Claim 20 provides a method which comprises increasing apoptosis in a cell by contacting the cell with C_6-ceramide and paclitaxel. Claim 25 provides a method which comprises decreasing the size of a tumor by contacting the tumor cells with C_6-ceramide and paclitaxel. Claim 30 provides a pharmaceutical composition comprising C_6-ceramide and

paclitaxel which causes apoptosis of a particular type of cancer cell.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Applicants maintain that the references cited against the rejected claims fail to support a *prima facie* case of obviousness, in that they fail to create a reasonable expectation of success.

Without experimentation, one of ordinary skill cannot reasonably predict that a successful anti-cancer outcome, not to mention a synergistic outcome, will occur using a *particular combination of two drugs*, even though each drug, when used individually, has anti-cancer effects.

Applicants respectfully point out that the Examiner herself agrees that combination therapy is unpredictable as set forth in her argument on page 9 of the instant Office Action, wherein the Examiner cites column 1, lines 28-37, of U.S. Patent No. 6,664,288 which recites as follows:

> "Combination therapies, while desirable, are a hit or miss proposition. The treatments are typically not additive. In many cases, cross effects and

> treatment load can result in lower effectiveness for the combinations, than either treatment alone."

In other words, each specific combination of two or more anti-cancer agents must be tested before one of skill in the art can know that such combination will be effective against cancer, let alone more effective than either agent alone. The Examiner has failed to show otherwise.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 20, 25, 26, 30 and 31-33 over these references.

Joshi et al. in view of Hartfield et al.

The Examiner rejected claims 20, 22-25 and 27-31 under 35 U.S.C. §103(a) as allegedly unpatentable over Joshi et al. (U.S. Patent No. 6,841,537) in view of Hartfield et al.

The Examiner stated the following regarding Joshi et al. Joshi et al. teaches a method of cancer therapy where the cancer cells are transformed with nucleic acids that encode gene products to inhibit growth of the cancer cells. The method includes administering to a cancer patient a nucleic acid that transforms the cancer cells and inhibits their growth by inducing apoptosis; and further administering paclitaxel as a cell cycle synchronizer to enhance the effect of the foreign therapeutic gene. In addition, the paclitaxel is in a liposomal formulation of instant claims 23 and 29, of which ceramide is listed as an example. Joshi et al. teach the administration techniques of instant claims 24 and 29 at col. 16, lines 60 *et seq.* of the specification, including intravenous injection. Joshi et al. teach the treatment of

human colon adenocarcinoma, human ovarian carcinoma, mouse melanoma, lung carcinoma, of the Markush groups of claims 20, 25, 30, and 31. The Examiner admitted that Joshi et al. does not teach C6-ceramide specifically.

The Examiner stated the following regarding Hartfield et al. Hartfield et al. teaches that C6-ceramide induces apoptosis in PC12 cells (an adrenal tumor cell line). The reference also teaches that ceramide, C6-ceramide, and C2-ceramide have the same efficacy for inducing apoptosis.

The Examiner stated that substitution of C6-ceramide from Hartfield et al. for the ceramide in the method disclosed by Joshi et al. would have been obvious because Hartfield et al. teaches that C6-ceramide and ceramide have the same efficacy for inducing apoptosis in PC12 cells. The Examiner asserted that therefore, these may be considered to be art-accepted equivalents.

In response, applicants respectfully traverse. Applicants contend that the references cited against the rejected claims fail to support a *prima facie* case of obviousness, in that the references, when combined, do not teach all elements of the claimed method.

Applicants note that contrary to the Examiner's assertions, Joshi et al. does not describe the use of ceramide. Instead, Joshi et al. teaches the use of different compounds, i.e. PEG-ceramides, namely PEG-ceramide-C8, PEG-ceramide-C14 and PEG-ceramide-C20, which the Examiner has not shown are the equivalent of ceramide, let alone C6-ceramide. Therefore, contrary to the Examiner's assertions, the PEG-ceramide

compounds described in Joshi et al. are not art-accepted equivalents of the ceramides described in Hartfield et al. based on the Examiner's showing.

In addition, Joshi et al. say nothing about using the PEG-ceramides to cause cell death. Instead, in Joshi et al., their sole purpose is to be used as vehicles for transporting paclitaxel into the cell.

Thus, Joshi et al. and Hartfield et al., in combination, fail to teach or suggest all elements of the claimed invention. It follows that these references also fail to provide a motive to combine and a reasonable expectation of success.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 20, 22-25 and 27-31 over these references.

Spencer et al. in view of Cai et al.

The Examiner rejected claims 20-33 under 35 U.S.C. §103(a) as allegedly unpatentable over Spencer et al. in view of Cai et al.

The Examiner stated the following regarding Spencer et al. Spencer et al. teaches that paclitaxel has in vitro as well as in vivo toxicity against several human cancer cell lines, including breast carcinoma, metastatic breast cancer, cervical cancer, colon carcinoma, endometrial carcinoma, glioma, head and neck squamous cell carcinoma, leukemia, neuroblastoma, non-small cell lung cancer, ovarian carcinoma, pancreatic carcinoma, prostate cancer, small cell lung cancer, non-Hodgkin's lymphoma, and multiple myeloma. The reference also

reviews paclitaxel therapy in phase I and II trials in patients with advanced breast cancer, advanced ovarian cancer, metastatic head and neck squamous cell carcinoma, non-small cell lung cancer, small cell lung cancer, non-Hodgkins lymphoma. Regarding claims 23 and 28, Spencer et al. teaches that paclitaxel is poorly soluble in water; therefore it is formulated in a vehicle of 50% polyoxyethylated castor oil (i.e., the common name for "Cremophore") and 50% alcohol (ethanol). Spencer et al. also teaches combination therapy with paclitaxel and several other agents, such as cisplatin, cyclophosphamide, doxorubicin, hydroxyurea, and dexamethasone. The reference teaches that the effectiveness could be additive or synergistic (greater than additive). For example, the effect was greater than additive in ovarian cancer cells when paclitaxel was administered prior to cisplatin; the effect was additive in human lung or breast cancer cells. The Examiner admitted that Spencer et al. does not teach combination therapy with C6-ceramide.

The Examiner stated the following regarding Cai et al. Cai et al. teaches that C6-ceramide kills both TNF-sensitive and TNF-resistant MCF7 cells through apoptosis. This reference does not teach paclitaxel.

The Examiner stated that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a combination of paclitaxel and C6-ceramide to treat breast carcinoma, metastatic breast cancer, cervical cancer, colon carcinoma, endometrial carcinoma, glioma, head and neck squamous cell carcinoma, leukemia, neuroblastoma, non-small cell lung cancer, ovarian carcinoma, pancreatic carcinoma, prostate cancer, small cell lung cancer, non-

Hodgkin's lymphoma, and multiple myeloma. The skilled artisan would have been motivated to combine paclitaxel and C6-ceramide, and would have had a reasonable expectation of success, having been taught by Spencer that it is known to use paclitaxel combination with conventional cancer treatments. The skilled artisan would have additionally been motivated to use a combination of paclitaxel and C6-ceramide having been taught by the prior art that paclitaxel in combination with other anti-cancer agents is known to show additive and/or greater than additive effects against various cancers (such as ovarian, breast, and lung cancer).

In response to the Examiner's rejection, applicants respectfully traverse and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Applicants maintain that the references cited against the rejected claims fail to support a *prima facie* case of obviousness, in that they fail to create a reasonable expectation of success.

Applicants again point out that without experimentation, one of ordinary skill cannot reasonably predict that a successful anti-cancer outcome, not to mention an outcome better than that seen using either agent alone, will occur using a *particular combination of two drugs*, even though each drug, when used individually, has anti-cancer effects.

Applicants again respectfully point out that the Examiner herself agrees that combination therapy is unpredictable as set forth in her argument on page 9 of the instant Office

Action, wherein the Examiner cites column 1, lines 28-37, of U.S. Patent No. 6,664,288, quoted above.

In other words, each specific combination of two or more anti-cancer agents must be tested before one of skill in the art can know that such combination will be effective against cancer, let alone more effective than either agent alone. The Examiner has failed to show otherwise.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 20-33 over these references.

In view of the above, applicants maintain that claims 20-33 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, 1st paragraph

The Examiner rejected claims 20-33 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not provide enablement for increasing apoptosis in all cancer types listed in the Markush group of claims 20, 25, 30 and 31 of cancer cells or all types of tumor growth *in vivo*. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. However, the Examiner stated that the specification is enabling for a method of increasing apoptosis in leukemia (in Jurkat cells), breast cancer (in the cell lines MCF7), prostate cancer (in the cell line LnCap), colon cancer (in the cell line HT29), pancreatic

cancer (in the cell line RWP-2), and head and neck squamous cell carcinoma (in the cell line TU-138) with the combination of paclitaxel and C_6-ceramide.

In response, and without conceding the correctness of the Examiner's rejection, applicants note that amended claims 20, 25, 30 and 31 recite only the cancers which the Examiner concedes are enabled by the specification. Therefore, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, 2nd paragraph

The Examiner rejected claims 23 and 28 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner stated that claims 23 and 28 contain the trade name "cremophore."

In response, and without conceding the correctness of the Examiner's rejection, applicants note that amended claims 23 and 28 now recite the term "CREMOPHOR." Therefore, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

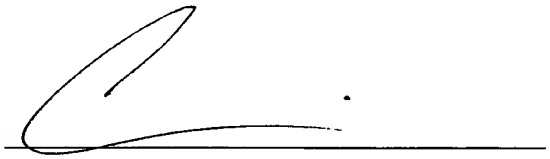
Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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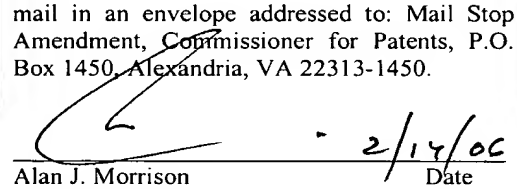

2/14/06

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